REMARKS

Status of the Claims

Claims 15, 18 and 19 are pending in the application. Claims 15, 18 and 19 are rejected. Claims 15 and 19 are amended herein. No new matter is added to the amended claims.

Claim amendments

Claim 15 is amended to overcome the 35 U.S.C. §112, first paragraph rejection. Amended claim 15 is drawn to a method of diagnosing a Wnt antagonist-associated lytic bone disease in an individual. Such a method comprises examining the expression of the human homologoue of Dickkopf-1 (DKK-1) protein in the individual, where an increased expression of the protein compared to that in a normal individual indicates that the individual has the risk of developing the Wnt antagonist-associated lytic bone disease (page 5, lines 7-21; Table 1; Example 9; Example 10; page 6, lines 1-4 and lines 17-21).

Claim 19 is amended to properly recite the limitation of claim 15. Amended claim 19 is directed to diagnosis of Wnt-antagonist associated lytic bone disease in an individual with multiple myeloma.

Objection raised in the Advisory Action

In the Advisory Action mailed May 8, 2006, the Examiner states that the proposed amendments filed by the Applicant in response to the Final Office

Action were not entered because the Examiner was of the opinion that the amendments would necessitate a new search and consideration with respect to patentability under 35 U.S.C. §112, first paragraph. The arguments made by the Applicant in the response after Final were not considered since they were drawn to the amendments that were not entered.

The claims are amended as discussed supra. The Wnt signaling pathway is critical for osteoblast differentiation and function. Targeted disruption of low-density lipoprotein 5 (LRP5) could lead to low bone mass phenotype and gain of function mutation in LRP5 could lead to high bone mass. Furthermore, DKK1 binds to LRP5/LRP6 and disrupts the Fz-LRP5/LRP6 association (page 20, line 1-page 21, line 19). Despite this information, it was not known whether DKK1 by itself or in combination with FRZB and LRP5 could lead to lytic bone disease.

Since multiple myeloma is associated with lytic bone disease and local bone destruction, the instant invention disclosed the expression of 12,000 genes in plasma cells of newly diagnosed multiple myeloma patients with or without lytic bone lesions. The instant specification teaches that two secreted Wnt signaling antagonists, SFRP-3/FRZB and DKK-1 were expressed in 40 of 47 plasma cells of multiple myeloma patients with lytic bone lesions and in only 16 of 28 plasma cells of multiple myeloma patients lacking bone lesions. Importantly, DKK-1 and FRZB were not expressed in plasma cells from 45 normal bone marrow donors of Waldenstrom's macroglobulinemia, a plasma cell malignancy that lacks bone disease (page 5, lines 7-21; Table 1; Examples 1, 9, 10). The

levels of expression of these genes were also consistent with the expression profile when examined immunohistochemically (Example 15).

Additionally, the instant invention also disclosed that serum derived from multiple myeloma patients with high DKK-1 blocked both Wnt signaling and osteoblast differentiation in vitro and that pre-incubation of serum with DKK-1 and FRZB antibodies inhibited this function (page 6, lines 1-4). The instant invention further teaches that the DKK-1 and FRZB inhibitors can be used to prevent bone loss in the general population (page 6, lines 17-21).

Further, the specification of the instant invention clearly states that the data presented therein demonstrates that the secreted Wnt-signaling antagonists, DKK-1 and FRZB mediate bone destruction seen in multiple myeloma. This along with the emerging evidence of an absolute requirement of Wnt-signaling in osteoblast growth and differentiation strongly implicate these factors in causing osteoblast anergy and contributing to multiple myeloma bone disease by suppressing the normal compensatory bone production that follows bone loss (page 17, line 16-page 18, line 2). The secreted DKK-1 and FRZB could account for both the systemic osteoporosis seen in multiple myeloma as well as the exaggerated local bone destruction proximal to plasma cells foci (page 18, lines 9-12). Thus, these genes could be used to predict extent of bone disease and future risk of developing bone disease (page 18, lines 15-18).

Furthermore, the instant specification also discusses a model that shows how DKK-1 expression by multiple myeloma plasma cells can be linked to multiple myeloma disease growth control and bone destruction (page 23, line 9-

page 24, line 17). Based on the above discussion, Applicant contends that the teachings of the instant specification demonstrate that DKK1 could be used to diagnose Wnt-associated lytic bone disease and therefore, the claim amendment does not raise any new matter. Hence, the amended claims comply with the 35 U.S.C. §112, first paragraph requirements. Accordingly, Applicant respectfully requests the Examiner to enter the amendments to the claim.

Since the Applicant's arguments in the response after Final mailed April 12, 2006 for the 35 U.S.C. §112, first paragraph rejection raised by the Examiner in the Final Office Action were not considered as they were drawn to the claim amendments that were not entered, this rejection is also addressed herein.

Claims 15 and 18-19 were rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. Applicant had respectfully traversed these rejections.

The Examiner stated that there was no reasonable guidance with respect to assessing the risk of any disease and/or disorder in the instant specification The Examiner cited **Chappuis** *et al.* and **McLaughlin** *et al.* that taught the importance of family history and environmental factors for cancer, which were the same while assessing the risk of a bone disease as taught by **Stevenson** *et al* to support the rejection. Furthermore, the Examiner stated that since the specification only suggested diagnosis of bone disease in multiple myeloma patient and lacked teaching of the use of this method in determining the risk of developing any and/or all bone disease, undue experimentation would be required to practice the invention as broadly claimed.

Applicant has amended claim 15 as discussed supra which no longer recites a method of determining the risk of developing a bone disease. Instead, the amended claim is now drawn to diagnosing a Wnt antagonist-associated lytic bone disease in an individual.

As discussed supra, the amended claim is supported by the teachings in the instant specification. Applicant respectfully submits that "the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue amount of experimentation. Because only an enabling disclosure is required, Applicant need not describe all actual embodiments" (M.P.E.P. 2164.02). In this case, the diseases such as multiple myeloma, osteoporosis, post-menopausal osteoporosis, malignancy-related (prostate cancer metastasis, breast cancer metastasis) bone loss are known in the art to be associated with bone lysis. Given the teaching in the instant specification, one skilled in the art can easily diagnose an individual suffering from any one of these diseases with Wnt antagonist-associated lytic bone disease by comparing the expression level of DKK-1 protein of such individuals with the expression of the protein of normal individuals.

Further, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with the information known in the art without undue experimentation (M.P.E.P. 2164.01). As discussed supra, Applicant submits that the instant specification has provided sufficient enablement for using the claimed method to identify individuals having a risk of developing lytic bone disease. Thus, the scope of the claimed

invention is commensurate with the enablement provided. Based on the above-mentioned amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 15, 18 and 19 under 35 U.S.C. §112, first paragraph.

This is intended to be a response to the Advisory Action mailed May 8, 2006 and the Final Office Action mailed January 12, 2006. Applicant also encloses a Petition for Extension of Time (1 month) along with this response. Please charge the $60 extension fee to the credit card identifed on the Form PTO-2038 enclosed with the response. Applicant submits that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
713-270-5391 (tel.)
713-270-5361 (facs.)
badler1@houston.rr.com